

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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:
: 04 md. 1603 (SHS)
:
: This document relates to:
: 06 Civ. 13095 (SHS)
In re: : 07 Civ. 03972 (SHS)
OXYCONTIN ANTITRUST LITIGATION : 07 Civ. 03973 (SHS)
: 07 Civ. 04810 (SHS)
:
: **CONFIDENTIAL-**
: **SUBJECT TO PROTECTIVE**
----- x **ORDER**

**MALLINCKRODT'S BRIEF ON THE UNENFORCEABILITY
OF U.S. PATENT NOS. 5,549,912, 5,656,295,
AND 5,508,042 DUE TO INEQUITABLE CONDUCT**

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INTRODUCTION

This case requires the Court to decide whether Purdue engaged in inequitable conduct in procuring the three patents in suit. This requires identifying acts of misrepresentation or omission, their materiality, and Purdue's intent. In the immortal words of The Beatles, the inequitable conduct in this case is here, there, and everywhere. It is highly material. And the only explanation for it is an intent on Purdue's part to deceive the patent examiner in order to secure, for years to come, its lucrative monopoly on controlled-release oxycodone.

In the *Endo* case, the Court focused on but one type of deception: Purdue's repeated misleading representations to the Patent Office regarding the supposed finding that the controlled-release oxycodone product of the patents acceptably controls pain over a four-fold dosage range, in contrast to the eight-fold dosage range purportedly required with other opioid analgesics. Ex. 1, * *Purdue Pharma L.P. v. Endo Pharmaceuticals, Inc.*, No. 00-civ-0829, 2004 U.S. Dist. LEXIS 10 (S.D.N.Y. Jan. 5, 2004). On appeal, the Federal Circuit agreed that it was misleading that Purdue failed to disclose that its representations about the four-fold dosage range were based on "insight" rather than empirical evidence. *Purdue Pharma L.P. v. Endo Pharmaceuticals, Inc.*, 438 F.3d 1123, 1131 (Fed. Cir. 2006). The court nevertheless held that, while material, the level of materiality was "not especially high" and remanded the case for further consideration of the issue of Purdue's intent. *Id.* at 1133, 1135. Following the Purdue-Endo settlement, it is left to new challengers—including Mallinckrodt—to pick up the cudgel and explain why Purdue's patents must be held unenforceable.

Until now, the court opinions have focused on just one act of misconduct—Purdue's failure to disclose that its statements about the four-fold dosage range (as compared to an eight-

* Citations to "Ex. __" refer to exhibits to the Declaration of Casey B. Howard in support of Mallinckrodt's Brief on the Unenforceability of U.S. Patent Nos. 5,549,912, 5,656,295, and 5,508,042 Due to Inequitable Conduct.

fold range) were not based on empirical evidence. But there is additional evidence of affirmative misrepresentations about purported “surveys” that support that purported discovery. Further, there is compelling evidence of numerous additional misrepresentations and concealment of material facts that, taken together, establish an unmistakable pattern of intentional deception of the Patent Office. Particularly—

- Purdue failed to disclose clinical trial results that squarely contradicted the claims of the patents in suit.
- Purdue falsely represented that it “surprisingly found” that a controlled-release oxycodone composition having an early peak plasma level would provide patients with 12 hours of pain relief when it had already made the same finding with respect to four of its own prior-art extended-release opioid compositions.
- The declaration of Robert Kaiko, which Purdue submitted to the PTO in an attempt to get its ‘331 patent allowed over close prior art, was drafted in a style to make it seem as if Kaiko were an independent expert, and did not reveal, among other things, that Kaiko’s employer, Purdue, was a corporate affiliate of the assignee of the application, and that Kaiko worked closely with the inventors of the patent.
- And, Purdue failed to disclose to the PTO the prior-art ‘598 patent, which was a reference that, together with the prior-art ‘341 patent, was found to render the claims of the ‘331 patent *prima facie* obvious.

These additional acts represent a heightened level of materiality than the evidence previously considered by the Court, and their pattern and pervasiveness demonstrate an intent to deceive that is as self-evident as it is pernicious.

STATEMENT OF FACTS

- A. Background: Long before patents in suit were filed, Purdue develops four different controlled-release drug products that have an early peak plasma level and provide 12 hours of pain relief.**

Although Purdue was to call its discovery of the controlled-release oxycodone product at issue here “surprising,” at least four opioid drug products that Purdue had earlier developed had

the same early (*i.e.*, within two to four hours of ingestion) peak plasma level (T_{\max}) in the bloodstream and provided most patients with 12 hours of pain relief.

1. **MS Contin[®]**

In the early 1980s, Purdue's English affiliate, Napp Laboratories, created an extended-release morphine formulation using a particular controlled-release system or "matrix" that it called the Contin system. (Ex. 2, *Endo Tr.* at 459:12-24, 477:4-5, 508:4-6 (Oshlack); Ex. 3, DTX 2194.) Purdue's clinical trials confirmed that the resulting drug, called MS Contin[®], provided 12 hours of pain relief in patients with chronic pain. (Ex. 4, DTX 3284 at P 382607; Ex. 5, DTX 3286 at P 505446.)

Stewart Leslie, a scientist at Purdue's affiliate, held two patents on the Contin controlled-release matrix used in MS Contin[®]. (Ex. 2, *Endo Tr.* at 508:10-14 (Oshlack); *see also* Ex. 6, U.S. Patent No. 3,965,256, issued June 22, 1976 (covering the Contin system); Ex. 7, U.S. Patent No. 4,235,870, issued November 25, 1980 (same).)

Purdue filed a new drug application for MS Contin[®] in 1985 and received final FDA approval in 1987. (*See* Ex. 8, DTX 3278 at P 238680; Ex. 9, Excerpts from FDA Orange Book.)

In the academic literature and in its marketing materials, Purdue boasted that MS Contin[®] exhibited an early T_{\max} (*i.e.*, between 2-4 hours) and gave 12 hours of pain relief, thereby providing early and long-lasting relief. (Ex. 2, *Endo Tr.* at 367:11-367:20, 377:7-380:3 (Kaiko); *see, e.g.*, Ex. 10, DTX 3260 at P 041767, P 041769, P 041772; Ex. 11, DTX 2766.)

MS Contin[®] has been a rousing success for Purdue, generating more than \$1.3 billion in sales from 1989 to 2002. (Ex. 12, PTX 877A.)

2. **Dihydrocodeine**

One good turn deserves another, and Purdue's success with MS Contin[®] motivated it to apply the same early T_{\max} , 12-hour-dosing model to a related opioid analgesic, dihydrocodeine.

The controlled-release dihydrocodeine formulation that Purdue developed copied the MS Contin[®] profile and had similar *in vivo* effects (*i.e.*, 2-4 hour T_{max} and 12-hour analgesic effect).

In May 1987, the attorney Harold Steinberg filed an application on Purdue's behalf for a patent on this controlled-release dihydrocodeine. (Ex. 2, *Endo* Tr. at 1608:14-20 (Steinberg).) Despite Purdue's previous success in formulating MS Contin[®] as a 12-hour drug with an early T_{max} , the inventors expressed "surprise" that the same result translated to dihydrocodeine: "The present inventors have surprisingly found that, in the case of dihydrocodeine, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief...." (Ex. 13, DTX 2047, U.S. Patent No. 4,834,984 ("the '984 patent") at col. 2, lns. 18-21.) The patent specification, in contrast, called it "usual," when seeking a 12-hour therapeutic effect, to produce a formulation that gives a peak plasma level of the drug between 4 and 8 hours after ingestion. (*Id.* at col. 2, lns. 13-18.)

The patent issued in 1989. (*See id.*) Its claims define controlled-release dihydrocodeine, in part, by its *in vitro* dissolution profile and its T_{max} between 2 and 4 hours. (*Id.* at col. 8, lns. 9-11) (claiming a dosage form where the "peak plasma level of dihydrocodeine obtained *in vivo* occurs between 2 and 4 hours after administration...").

3. *Hydromorphone*

Purdue was on a roll. In October 1987, five months after filing the dihydrocodeine application, Purdue applied for a patent on yet another controlled-release opioid analgesic, hydromorphone. (*See* Ex. 14, DTX 2063, U.S. Patent No. 4,844,909 ("the '909 patent").) With this drug, too, Purdue copied the MS Contin[®] profile with a 2-4 hour T_{max} giving 12 hours of therapeutic effect. (*Id.* at col. 2, lns. 16-19.) Purdue obtained a patent on this formulation in 1989, U.S. Patent No. 4,844,909. (*Id.*) Purdue also obtained a continuation patent in 1991,

which issued as U.S. Patent No. 4,990,341. (Ex. 15, DTX 2045, U.S. Patent No. 4,990,341 (“the ‘341 patent”).)

Not only did this hydromorphone product copy the *in vivo* profile of MS Contin[®] and dihydrocodeine, but Steinberg also copied the words used in the dihydrocodeine patent application to describe that profile: “The present inventors have surprisingly found that, in the case of hydromorphone, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief.” (Ex. 2, *Endo* Tr. at 1608:4-9, 1609:1-19 (Steinberg); Ex. 15, DTX 2045, the ‘341 patent at col. 2, lns. 19-22; Ex. 13, DTX 2047, the ‘984 patent at col. 2, lns. 18-29.) And once again, Purdue’s inventors asserted that, in contrast, a peak plasma level between 4-8 hours after administration was “usual in the pharmaceutical art” to obtain a 12-hour therapeutic effect. (Ex. 15, DTX 2045, the ‘341 patent at 14-19.)

This ‘341 patent also defines controlled-release hydromorphone, in part, by its *in vitro* dissolution profile and its T_{\max} between 2 and 4 hours. (Ex. 15, DTX 2045, the ‘341 patent at col. 9, ln. 18-col. 10, ln. 18.)

4. Codeine

By 1987 at Purdue, Benjamin Oshlack, one of the named inventors of the patents in suit, developed a controlled-release form of codeine. (Ex. 2, *Endo* Tr. at 479:23-480:4 (Oshlack); Ex. 16, PTX 498.) This formulation also had a peak plasma level at between 2 and 4 hours (3.3 hours) and a duration of action of 12 hours. (Ex. 17, DTX 2706 at P 486912.)

B. Purdue develops oxycodone formulation with an early T_{\max} and having 12-hour pain relief.

1. Development of the formulation.

Purdue’s two patents on the Contin matrix were due to expire in 1993 and 1997, and Purdue had no other patents covering the MS Contin[®] formulation or the effect that MS Contin[®]

would have in the human body. (*See* Ex. 6, the '256 patent; Ex. 7, the '870 patent.) Thus, once the Contin patents expired, MS Contin[®] would be vulnerable to generic competition.

Although Purdue had done some development work on a controlled-release form of oxycodone in the 1980s, Purdue's interest in this drug product heightened after the pharmacologist Dr. Robert Kaiko arrived at Purdue in 1985. (Ex. 2, *Endo* Tr. 166:19-167:5 (Kaiko).)

Kaiko became the champion at Purdue of developing controlled-release oxycodone. In July 1990, he wrote a memorandum to members of Purdue's top management summarizing the case for pursuing further development and marketing of controlled-release oxycodone: (*See* Ex. 18, DTX 3165.) Among other things, Kaiko said:

MS Contin may eventually face such serious generic competition that other controlled-release opioids must be considered.

While we are "going laterally" with MS Contin to non-cancer pain indications, it would be unwise to "put all of our eggs into the MS Contin basket" in face of the prospect of generic MS Contin competition that would "crush all of the analgesic eggs."

While we have reason to believe that other pharmaceutical firms are formulating controlled-release morphine and controlled-release hydromorphone, there is no evidence to date that this is being done with oxycodone. A controlled-release oxycodone is, thus, less likely to initially have generic competition.

(*Id.* at P 644252-53.)

Kaiko wrote a series of memos outlining the expected properties of controlled-release oxycodone and its theoretical advantages over morphine as a controlled-release drug, including a "short elimination half life" (allowing for steady state to be reached earlier) (Ex. 18, DTX 3165 at P 664252) (Ex. 2, *Endo* Tr. 442:2-10 (Kaiko)), and higher bioavailability. (Ex. 2, *Endo* Tr. 444:16-21 (Kaiko); Ex. 19, DTX 3156 at P 037161.) This, in turn, would translate to a number

of desirable clinical outcomes, including “the finding that a narrower range of dosages of oxycodone are required...than with the utilization of drugs with a lower oral bioavailability” and a “shorter time to titration to the ‘right dose.’” (Ex. 20, DTX 3629 at P 037082-83.) He concluded that any drug with less variation in bioavailability than controlled-release morphine would be expected to exhibit “less variation in pain control.” (Ex. 21, DTX 3735 at P 037163.)

These and other internal Purdue documents reflect that the authors’ beliefs about the expected properties and advantages of controlled-release oxycodone were based solely on theories and predictions and not clinical proof:

- “While the *theoretical argument* may be relatively strong using available data, it may be difficult to demonstrate these claims within the context of efficacy studies.” (Ex. 18, DTX 3165 at P 644253.)
- “This is a *theory not yet proven, we will have to see.*” (Ex. 19, DTX 3156 at P 037159 (hand-written note).)
- “While one *would predict* [that fewer patients will be inappropriately dosed upon initiation of OxyContin®] based on [oxycodone’s] unique combination of a high oral bioavailability and short half-life, *this claim would need to be clinically demonstrated.*” (Ex. 21, DTX 3735 at P 037163.) (All emphases added.)

In developing controlled-release oxycodone, Oshlack and Kaiko wished to obtain the same T_{\max} and duration of action as MS Contin®, *i.e.*, 12 hours of therapeutic activity and a peak plasma level at between 2 and 4 hours. Their starting point was to copy as closely as possible the *in vitro* dissolution profile of MS Contin®. (Ex. 2, *Endo Tr.* at 570: 24-571:14 (Oshlack).) Kaiko had a “reasonable expectation that with [a] dissolution profile matched to MS Contin®,” controlled-release oxycodone would also be “a 12-hour, twice-a-day drug.” (*Id.* at 178:5-179:14 (Kaiko).) Oshlack likewise had a “reasonable expectation” that the dissolution profile would result in a drug that gave 12 hours of pain relief. (*Id.* at 571:9-14 (Oshlack).)

In his initial formulation work with oxycodone, Oshlack had found that he could not use the Contin controlled-release system because formulations using that system dissolved too quickly. (Ex. 22, DTX 3272; Ex. 2, *Endo* Tr. at 492:6-493:5 (Oshlack).) In place of the Contin system, Oshlack developed his own controlled-release matrix that came to be known as the AcroContin system. (*Id.*) Using this system, Oshlack prepared a controlled-release oxycodone formulation that displayed the same *in vitro* dissolution profile as MS Contin®. (Ex. 22, DTX 3272.) Initial tests of that formulation in humans showed that it reproduced the early T_{max} of MS Contin®. Oshlack and Kaiko had succeeded—and on their first try. (Ex. 2, *Endo* Tr. 289:20-291:3 (Kaiko).)

C. Purdue obtains patents-in-suit directed to controlled-release oxycodone but makes numerous misrepresentations to do so.

In 1986, *i.e.*, before he filed the patent applications on controlled-release dihydrocodeine and hydromorphone, the attorney Steinberg filed a patent application on behalf of Oshlack for the AcroContin controlled-release system. The patent issued on August 29, 1989 as U.S. Patent No. 4,861,598, for “Controlled Release Bases for Pharmaceuticals.” (Ex. 23, DTX 2048, U.S. Patent No. 4,861,598 (“the ‘598 patent”).) According to the ‘598 patent specification, it can be difficult to achieve the desired delay in release of highly soluble active ingredients such as oxycodone with conventional controlled-release systems. (*Id.* at col. 4, lns. 17-23.) Oshlack’s AcroContin system, however, “provide[s] sustained release of therapeutically active ingredients over a period of time from five hours and for as much as 24 hours after administration....” (*Id.* at col. 3, lns 27-29.) The specification describes “a strong correlation...between the *in vitro*...dissolution time and the *in vivo* bioavailability,” and describes a number of drugs that, when formulated with Oshlack’s system, display extended dissolution times. (*Id.* at col. 2, lns.

48-51; col. 8, lns. 36-42.) The '598 patent specifically claims controlled-release oxycodone made with the AcroContin system. (*Id.* at col. 8, ln. 40, 65-66.)

The '598 patent would not, however, prevent others from making controlled-release oxycodone products with an early T_{\max} and 12-hour pain relief using other controlled-release systems. Accordingly, Purdue, with the assistance of the same attorneys who had prosecuted the applications for the '598 patent and the earlier '341 and '984 patents on controlled-release hydromorphone and dihydrocodeine, set out to obtain additional patents that would provide broader protection from competition by claiming, among other things, the early T_{\max} property.

1. The '331 oxycodone application does not disclose the '598 oxycodone patent

As the Court is aware, U.S. Patent No. 5,266,331 is the parent to the three patents in suit. (Ex. 24, DTX 2044, U.S. Patent No. 5,266,331 ("the '331 patent").) The '331 application, filed November 1991, discloses examples of oxycodone formulations using the AcroContin system claimed in the '598 patent. Example 3 of the '331 application is the formulation used in the OxyContin[®] product. (Ex. 2, *Endo* Tr. 496:24-497:16 (Oshlack); Ex. 25, PTX 1009 ('912 patent examples 1-3, 5, 6 correspond to '331 patent examples 1-5); Ex. 24, DTX 2044, the '331 patent at col.7, ln. 30-col. 8, ln. 25.) The '598 patent also covers the formulation of OxyContin[®]. (Ex. 26, DTX 4110 at P 650651.)

The '331 application claimed "surprise"—that word again—that the same dissolution profile disclosed in the '341 hydromorphone patent could now be used for oxycodone, even though an oxycodone composition fitting that profile had been disclosed in the prior-art '598 patent. (Ex. 27, PTX 7 at '331-6; Ex. 23, DTX 2048, the '598 patent at col. 6, lns. 40-51.) In the specification of the '331 application, the inventors said that they did not think they could develop a controlled-release oxycodone product with the dissolution rate disclosed in the hydromorphone

'341 patent. (Ex. 27, PTX 7 at '331-5 - '331-6.) They said: "controlled release compositions containing other therapeutically active agents having the same medicinal use (analgesia) and structurally related to hydromorphone, such as oxycodone, were not believed to be obtained when using similar techniques as those set forth in [the '341 patent]." (*Id.*)

But the prior-art '598 patent expressly discloses a "firmly established" correlation between *in vitro* dissolution properties of a controlled-release composition and its *in vivo* therapeutic effect. (Ex.23, DTX 2048, the '598 patent at col. 2, lns. 47-55.) The patent also explained that, "[i]n view of this relationship, it is clear that the dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating slow release compositions." (*Id.* at col. 2, lns. 55-59.)

Moreover, in the prior-art '598 patent, Oshlack had disclosed extended-release oxycodone with a release rate squarely within the listed dissolution-rate ranges taught in the '341 patent (*compare* Ex. 23, DTX 2048, the '598 patent at col. 6, lns. 40-51 *with* Ex. 15, DTX 2045, the '341 patent at claim 1, col. 9-ln. 18- col. 10, ln.2), yet called these very same ranges "surprising" in the '331 patent application (Ex. 27, PTX 7 at '331-6).

Neither Oshlack nor Steinberg (the prosecuting attorney on the '598, '331, and '341 patents) disclosed the '598 patent to the PTO in the application for the '331 patent. (Ex. 2, *Endo* Tr. at 1598:17-21; 1608:4-9; Ex. 23, DTX 2048, the '598 patent.)

2. Purdue represents the existence of other surprising results.

Although Purdue did not disclose the '598 patent, the examiner found it anyway and in April 1992 issued an obviousness rejection citing the combination of the '598 and '341 patents. (Ex. 27, PTX 7 at '331-35 - '331-36.) Purdue responded by changing tactics—it walked away from the assertion that the dissolution profile of OxyContin® was "surprising." Instead, it found another "surprise" to peddle to the Patent Office in trying to get the '331 patent allowed.

Specifically, in response to the obviousness rejection, Davidson, an attorney at Steinberg's law firm, described to the Patent Office a purported problem never even identified in the '331 application, namely that "surveys" had suggested that it took an eight-fold dosage range of opioid analgesics in order to control pain:

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

(Ex. 27, PTX 7 at '331-40 (emphasis omitted))

Redacted But now, according to Purdue, its invention "surprisingly" solved that purported problem: "It has now been *surprisingly discovered* that the presently claimed controlled release oxycodone formulations acceptably control pain over a *substantially narrower, approximately four-fold* (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general." (Ex. 27, PTX 7 at '331-41 (first emphasis added).)

The claim of "surveys" of other opioid analgesics documenting the purported eight-fold range and resulting titration problem was apparently overstated and was certainly never documented by Purdue. When questioned, Kaiko said that there were not "surveys" of other opioid analgesics but rather just one survey, and of only one opioid analgesic, morphine. (Ex. 2, *Endo Tr.* at 222:1-10.) Neither Kaiko nor any other representative of Purdue has ever provided any evidence of this purported survey of morphine.

Notwithstanding Purdue's lack of empirical proof, its response to the rejection went on in great detail to extol the "important clinical advantages" that this purported narrower range had been found to deliver:

The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

(Ex. 27, PTX 7 at '331-42.) The response concluded: "[o]ne skilled in the art would certainly not arrive at this surprising result without the benefit of hindsight." (*Id.* at '331-43.)

The examiner, apparently dissatisfied with mere attorney argument, issued in February 1993 a second office action rejecting the proposed claims. (*Id.* at '331-44 - '331-46.) Steinberg then had an interview with the examiner. The summary record of that interview reveals that the "[a]pplicant will submit proposed declaration supporting unobviousness and unexpected results." (*Id.* at '331-47.)

In March 1993, after the interview, Steinberg submitted a response to the second office action, as well as a declaration of Kaiko describing Kaiko as "a person truly skilled in the art." (*Id.* at '331-49.) Although the statements in Kaiko's declaration were couched in the style of an independent expert's declaration ("I believe that my experience...establishes me as an expert in the pharmacology of opioid analgesics." (*Id.* at '331-53)), Kaiko was not an independent expert; he was employed by Purdue, an affiliate of Euro-Celtique, the patent's assignee, and owned by the same people who owned Purdue. (*Id.* at '331-51.) But the declaration did not disclose Kaiko's interest. (*See id.* at '331-51 - '331-56.) It did not disclose the relationship between Purdue and Euro-Celtique. (*See id.*) It did not disclose that Kaiko was a co-worker of the inventors. (*See id.*) It did not disclose that Kaiko had personally participated in reducing the

claimed invention to practice. (*See id.*) And it did not disclose that Kaiko was a named co-inventor on a different patent application relating to the same alleged invention. (*See id.*)

Kaiko's declaration averred, among other things, that "one skilled in the art having information concerning the time to reach peak plasma concentration...[T_{max}]...and duration of effect for a controlled release *hydromorphone* formulation as set forth in the...'341 patent, could not predict whether a controlled release *oxycodone* formulation having a T_{max} in 2-4 hours would also provide a duration of therapeutic effect of at least 12 hours." (*Id.* at '331-54.) (Emphasis in original). Kaiko concluded that it was his "opinion that one skilled in the art would not arrive at the presently claimed invention by combining the teachings" of the '341 and '598 patents. (*Id.* at '331-56.)

Kaiko's declaration included an attachment that stated, among other things:

[The invention] acceptably controls pain over a substantially narrower, approximately four-fold (10 to 40 mg q 12h around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general....

(*Id.* at '331-59). The attachment concluded by stating that the "clinical significance" of this four-fold dosage range compared to opioids requiring twice the dosage range was "the most efficient and humane method of managing pain requiring repeated dosing," *i.e.*, an improved titration process, because "the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced." (*Id.* at '331-60.)

Following receipt of Kaiko's declaration, the examiner allowed all the pending claims, and the '331 patent issued on November 30, 1993. (*Id.* at '331-84; Ex. 24, DTX 2044.)

3. Purdue repeats misrepresentations in the applications for the patents in suit.

In November 1992, Purdue filed a patent application that issued as the '912 patent and gave rise to its two siblings, the '295 patent (a continuation-in-part of the '912) and the '042 patent (a division of the '912), *i.e.*, the three patents in suit here. (Ex. 29, DTX 2049 U.S. Patent No. 5,549,912 ("the '912 patent"); Ex. 30, DTX 2059, U.S. Patent No. 5,656,295 ("the '295 patent"); Ex. 31, DTX 2060, U.S. Patent No. 5,508,042 ("the '042 patent").)

The '912 application listed Kaiko as an inventor. (Ex. 29, DTX 2049, the '912 patent.) It was filed months before Kaiko would file a declaration in the '331 patent prosecution implying that he was a disinterested independent expert. (*Id.* (filed November 1992)); Ex. 27, PTX 7 at '331-51 (submitted March 1993).)

a. Reduced dosage range and ease of titration

Having relied on representations about dosage-range reduction and ease of titration in responding to office actions regarding the '331 application, the inventors and their attorneys added those assertions to the specifications of the patents in suit, each of which recites an extended-release oxycodone composition that provides pain relief using a four-fold range of dosages as compared to an alleged eight-fold range needed for other opioid compositions. These patents identify the same purported "surveys" of other opioid analgesics—actually one purported survey of morphine of which no evidence has ever been produced—that Purdue discussed in its response to the obviousness rejection during prosecution of the '331 patent, and the same "surprising" solution to the purported problem:

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients.

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

(Ex. 27, PTX 7 at '331-40; Ex. 29, DTX 2049, the '912 patent at col. 1, lns. 10-13, col. 3, lns. 34-41; Ex. 30, DTX 2059 the '259 patent at col. 1, lns 10-13, col. 3, lns. 34-41; Ex. 31, DTX 2060 the '042 patent at col. 1, lns. 12-15, col. 3, lns. 38-45.)

The specifications also refer to the “clinical significance” of the “10 to about 40 mg” dosage range:

The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

(See Ex. 29, DTX 2049, the '912 patent at col. 4, lns. 58-63; Ex. 30, DTX 2059, the '295 patent at col. 4, lns. 58-63; Ex. 31, DTX 2060, the '042 patent at col. 4, lns. 60-65.)

b. Early T_{\max} and 12-hour pain relief

As in the '331 application, the applications for the three patents in suit assert that the inventors had “surprisingly found” that extended-release oxycodone compositions of the invention exhibited an early T_{\max} and provided for 12 hours of pain relief. (Ex. 29, DTX 2049, the '912 patent at col. 5, lns. 5-16; Ex. 30, DTX 2059, the '295 patent at col. 5, lns. 5-16; Ex. 31, DTX 2060, the '042 patent at col. 5, lns. 7-18.) But, as discussed above, Purdue, through the same prosecuting attorneys, had made the same claim of “surprise” about a 2-4 hour T_{\max} and 12 hours of pain relief in the dihydrocodeine patent and the hydromorphone patents. (Ex. 15, DTX 2045, the '341 patent at col. 2, lns. 14-26; Ex. 13, DTX 2047, the '984 patent at col. 2, lns. 13-21.) The language in the specifications of the asserted patents tracked almost exactly those earlier patents. The only significant difference was to insert the word oxycodone in place of the

prior-art opioids. (*Compare* Ex. 29, DTX 2049, the '912 patent at col. 5, lns. 5-16; Ex. 30, DTX 2059, the '295 patent at col. 5, lns. 5-16; Ex. 31, DTX 2060, the '042 patent at col. 5, lns. 7-18 with Ex. 15, DTX 2045, the '341 patent at col. 2, lns. 14-26; Ex. 13, DTX 2047, the '984 patent at col. 2, lns. 13-27.)

During prosecution of the '331 patent, Purdue's inventors also failed to disclose that the compositions of the '984 dihydrocodeine patent, the codeine Contin formulations, and MS Contin[®] all exhibit the early T_{\max} and 12-hour pain relief profile that the inventors of the patents in suit claimed was "surprising." (Ex. 13, DTX 2047, the '984 patent at col. 2, lns. 13-21; Ex. 17, DTX 2706 (showing a T_{\max} for codeine Contin of 3.3 hours).)

In the *Endo* trial, Kaiko conceded that he was "aware that there were several controlled-release opioid analgesic formulations that actually were characterized by a T_{\max} of 2 to 4," including both codeine and dihydrocodeine. (Ex. 2, *Endo* Tr. 377: 7-25 (Kaiko).) He also admitted that he was aware that Roxanal SR[®], a controlled-release oral morphine formulation, "also has a T_{\max} of between 2 and 4 hours." (*Id.* at 379:11-379:16 (Kaiko).) When asked why Purdue failed to cite this prior art to the PTO, he tried to downplay the significance of these references by suggesting that neither "controlled-release codeine or controlled-release dihydrocodeine" are "prescribed to treat moderate to severe pain." (*Id.* at 456:1-15 (Kaiko).)

This was untrue. The '984 dihydrocodeine patent explicitly states that it is for "moderate to severe pain" (Ex. 13, DTX 2047, the '984 patent at col. 1, lns. 5-7), and internal Purdue documents described controlled-release codeine as a direct competitor to controlled-release oxycodone for "moderate to moderately-severe cancer pain" (Ex. 32, DTX 3184 at P 775189).

Kaiko admitted, not only that he was aware of these prior-art formulations, but that his "lawyers appreciated this as well." (Ex. 2, *Endo* Tr. 369:20-370:5 (Kaiko).) Steinberg admitted

that he knew about the '984 dihydrocodeine patent but that he decided not to tell the Patent Office about it. (*Id.* at 1613: 10-21 (Steinberg).) When pressed, Steinberg contended that he didn't cite the '984 patent because he thought it was "cumulative" of the '341 hydromorphone patent. (*Id.* at 1632: 6-11 (Steinberg).)

c. The inventors asserted that a T_{\max} of 4-8 hours is usual.

The inventors also copied language from the '341 hydromorphone patent that a T_{\max} of 4-8 hours is "usual in the pharmaceutical art" for a 12-hour drug. (*See, e.g.*, Ex. 2, *Endo* Tr. 365:7-370:5 (Kaiko).) The record contains no evidence supporting that assertion.

4. The inventors failed to disclose clinical results that called into question oxycodone's reduced dosage range and ease of titration

On May 3, 1994, Kaiko, Oshlack, and others developing OxyContin[®] for Purdue received a memorandum regarding the "OxyContin Tablet Investigator Survey Preliminary Report" containing responses from physicians treating cancer patients with controlled-release oxycodone. (*See* Ex. 33, DTX 3739.) The cover memo explains that "the investigators' comments are important" because "they are actually using the drug." (*Id.* at P 054892.) The survey results showed that none of the 11 physicians responding to the survey found OxyContin[®] easier to titrate than MS Contin[®]. (*Id.* at P 054893.)

Purdue also directed and funded a study, the LoRusso study, that sought to compare controlled-release oxycodone to controlled-release morphine in cancer patients at 9 treatment centers. (Ex. 34, PTX 717 at P 187347-48, P 187368) The final LoRusso study report concluded that "[t]he median time to achieve stable pain control was two days with both treatments, and the number of dose adjustments required...were similar for both drugs." (*Id.* at P 187373.)

Kaiko was aware of the LoRusso study: he received a draft of the final study report, and on August 22, 1996 provided detailed comments, including a draft conclusion. (Ex. 35, DTX 4358.) Kaiko's draft conclusion stated that "CR oxycodone provided comparable efficacy as CR morphine with no significant differences in: number of dosage adjustments; time to stable pain control; degree of pain control; uses of rescue medication." (*Id.* at P 572294.)

Purdue obtained an abstract of the LoRusso study results on November 14, 1996. (Ex. 36 DTX 3738.) The abstract concludes that the time to stable pain control, reflecting the amount of time required to titrate the drug to the right dose, was basically the same for CR morphine and CR oxycodone. (*Id.*) Kaiko authored a journal article about the study in late 1997 that likewise concluded that OxyContin® and MS Contin® had comparable ease of titration. (Ex. 37, DTX 2844 at EN000276.)

Another study, commissioned by Purdue in 1993 and called the Kalso study, similarly concluded that there was no significant difference in time to stable pain control for controlled-release oxycodone and controlled-release morphine. (Ex. 38, DTX 4355 at P 642973.) The final study report concluded that "[i]n the titration period there were no significant differences between the CR oxycodone and CR morphine treatment groups with respect to the number of days required to achieve stable pain control." (*Id.* at P 642994) By August 16, 1996, Kaiko was aware of the conclusions in the final report. (Ex. 2, *Endo* Tr. 429:20-431:6 (Kaiko).)

Even though they contradicted the arguments made in favor of patentability of the asserted claims, Purdue did not submit any of these studies to the PTO.

D. As a result of Purdue's misrepresentations, PTO issues patents in suit.

In earlier briefs, Purdue has spent considerable effort arguing that the critical representations regarding the four-fold dosage range of controlled-release oxycodone versus the eight-fold range for other opioids and the resulting ease of titration had little significance in the

PTO's review and allowance of the '912, '042 and '295 patents. But the importance of these representations is evident in the file histories of the '912 and '042 patents.

With respect to the '912 application, the examiner issued an office action on August 22, 1994, rejecting the claims as anticipated by the '341 hydromorphone patent. (Ex. 39, PTX 4, at '912-114, '912-115.) In a response dated February 22, 1995, the prosecuting attorney Davidson first argued that the '341 patent was not an anticipating reference because it disclosed only controlled-release hydromorphone and not controlled-release oxycodone. (*Id.* at 119, 123-126.) In addition, and in apparent anticipation of a likely future rejection for obviousness, Davidson again asserted the purportedly "surprising discovery" of the four-fold dosage range and the "extreme clinical importance" of this "result" in terms of reduced pain and easier titration. (*Id.* at 122-23.) Moreover, Davidson told the Patent Office, these "surprising benefits...would not be obtained via the hydromorphone formulations of the '341 patent." (*Id.* at 124.) As noted earlier, Kaiko had no data to support this representation.

Meanwhile, Davidson had filed a divisional patent application that matured into the '042 patent. The same examiner who was also handling the '912 application issued no further rejections based on the prior art and allowed the '042 patent to issue on April 16, 1996. (*See generally* Ex. 39, PTX 4 and Ex. 40, PTX 6; Ex. 31, DTX 2060, the '042 patent.) In the notice of allowability, dated December 24, 1995, the examiner gave a statement of reasons for allowance: "None of the references of record singly anticipate or in combination motivate one with ordinary skill in the art to formulate the particular method for reducing the dosage of oxycodone as set forth in the claims." (Ex. 40, PTX 6 at '042-64.)

Similarly, the examiner allowed the '912 patent to issue on August 27, 1996, and the '295 patent to issue on August 12, 1997, having made no additional rejections based on the prior art. (See Ex. 29, 2049, the '912 patent; Ex. 30, DTX 2059, the '295 patent.)

ARGUMENT

Given the additional evidence discussed below, the Court should find the patents here unenforceable for inequitable conduct based solely on Purdue's representations about the four-fold vs. eight-fold dosage range. Nevertheless, the record is replete with numerous additional material misrepresentations and omissions all directly bearing on the issue of patentability—so many that it is unavoidable to conclude that Purdue intended to deceive the Patent Office.

I. Legal Standards

"Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [Patent] Office." 37 C.F.R. § 1.56(a) (2004); see also, *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed. Cir. 1995) (citing *Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co.*, 324 U.S. 806, 808 (1945) ("[a]pplicants for patents are required to prosecute patent applications in the PTO with candor, good faith, and honesty."). "A breach of this duty may constitute inequitable conduct, which can arise from an affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive or mislead the PTO." *Purdue Pharma LP v. Endo Pharmaceuticals, Inc.*, 438 F.3d 1123, 1128 (Fed. Cir. 2006).

The first element of proof is materiality, which is determined by the standard set forth in PTO Rule 56. *Id.* at 1129; see also 37 C.F.R. § 1.56(a) (2004). Under the version of that rule applicable here, "information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and:

- (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
- (2) It refutes, or is inconsistent with, a position the applicant takes in:
 - (i) Opposing an argument of unpatentability relied on by the [Patent] Office, or
 - (ii) Asserting an argument of patentability.

37 C.F.R. § 1.56(b) (2004). If a misrepresentation or omission is material, it does not matter whether the patent examiner in fact relied on it or whether the patent would have issued anyway. *Merck & Co., Inc. v. Danbury Pharmacal, Inc.*, 873 F.2d 1418, 1421 (Fed. Cir. 1989); *Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1366 (Fed. Cir. 2007).

The second element of proof is intent to deceive or mislead the Patent Office. *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 872 (Fed. Cir. 1988). Direct evidence of intent to deceive is normally not available and is by no means required. *Hoffman-LaRoche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1371 (Fed. Cir. 2003) (“a confession from the stand by the inventor or the prosecuting attorney” is not required). “[I]ntent to deceive is usually inferred from the facts and circumstances surrounding the conduct at issue,” *Cargill*, 476 F.3d at 1364, and intent “is most often proven by ‘a showing of acts the natural consequences of which are presumably intended by the actor.’” *Merck*, 873 F.2d at 1422 (citing *Kansas Jack Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983)). Finally, a pattern of repeated misrepresentation or withholding of material facts can also provide the requisite evidence of wrongful intent. *Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1193 (Fed. Cir. 1993).

Once threshold showings of materiality and intent have been made, the court must then “balance the equities to determine whether the patentee has committed inequitable conduct that warrants holding the patent unenforceable.” *Cargill*, 476 F.3d at 1364 (internal quotations omitted).

Finally, a finding of unenforceability based on inequitable conduct committed during prosecution of a parent application (such as the '331 patent) may also render unenforceable later patents (such as the '912, '295, and '042 patents) that issued from related applications. *See Consolidated Aluminum Corp. v. Foseco Int'l Ltd.*, 910 F.2d 804, 809-11 (Fed. Cir. 1990).

II. This Court can find inequitable conduct based solely on Purdue's statement or implication that experimental results supported its "finding" that a four-fold dosage range for controlled-release oxycodone distinguished the patent claims from the prior art.

The previous opinions in *Endo* focused solely on Purdue's argument to the PTO that a four-fold dosage range distinguished the invention over the prior art using language that implied that it had obtained experimental results, while omitting to tell the PTO that its discovery was based only on insight. The Federal Circuit found that because this was an omission, not an affirmative representation, its level of materiality was "not especially high." *Endo*, 438 F.3d at 1133.

There is, however, evidence not previously considered of actual *affirmative misrepresentations* with respect to the purported existence of empirical evidence supporting the claim that a four-fold dosage range distinguished the invention over the prior art. We discuss that in Part A of this section. Further, that additional evidence aside, a number of other factors unremarked by either this Court or the Federal Circuit constitute powerful indicia of an intent to mislead the Patent Office. That we discuss in Part B of this section.

A. Purdue misrepresented that it had "surveys" of opioid analgesics establishing that these analgesics required an eight-fold dosage range in order to control pain in about 90% of patients.

In order to convince the Patent Office that controlled-release oxycodone had unexpected and important benefits over other opioid analgesics in the prior art, Purdue contrasted the four-fold dosage range of controlled-release oxycodone required to control pain in 90% of patients

with the alleged eight-fold range required with other opioid analgesics. The common application for the '912, '042, and '295 patents stated, under the heading "Background of Invention":

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients.

(Ex. 39, PTX 4 at '912-7; Ex. 40, PTX 6 at '042-8; Ex. 41, PTX 5 at '295-8.) Then, under the subheading "Detailed Description [of the invention]":

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients *for opioid analgesics in general*.

(Ex. 39, PTX 4 at '912-11 - '912-12; Ex. 40, PTX 6 at '042-12 - '042-13; Ex. 41, PTX 5 at '295-13 (emphasis added).)

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The misrepresentations that surveys had been done were highly material because their purported results allowed Purdue to distinguish, in a single stroke, the claimed invention from the entire spectrum of prior-art controlled-release opioid drugs. They were also of substantial help to Purdue's counsel in distinguishing the prior-art hydromorphone compositions of the '341 patent. When, during prosecution of the '331 application, the examiner rejected the claims as obvious in light of the '341 patent and the '598 patent (Ex. 27, PTX 7 at '331-35, '331-36), Davidson told the Patent Office about the purported surveys of other opioid analgesics (*id.* at '331-42), and then compared the four-fold dosage range of controlled-release oxycodone to the purported eight-fold dosage range required with the controlled-release hydromorphone product of the '341 patent:

This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients *utilizing controlled release hydromorphone*, or controlled release opioid analgesics in general.

(*Id.* at '331-43 (emphasis added).) Later, in response to the first office action in the '912 prosecution, in which the examiner rejected the claims as anticipated by the '341 patent (Ex. 39, PTX 4 at '912-115), Davidson made essentially the same representation, stating that the "surprising benefits [of controlled-release oxycodone] would not be obtained via the hydromorphone formulations of the '341 patent." (*Id.* at '912-124.)

The high materiality of the representation regarding controlled-release hydromorphone is underscored by the examiner's statement of reasons for allowance of the '042 patent:

None of the references of record singly anticipate or in combination motivate one with ordinary skill in the art to formulate the particular method for reducing the dosage of oxycodone as set forth in the claims.

(Ex. 40, PTX 6 at '042-64.)

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Until the July 12, 2007 pretrial conference in this case, no one had raised the issue of the non-existent surveys of opioids other than morphine. After Mallinckrodt did so (Ex. 44, July 12, 2007 Hearing Tr. at 20:10-21:8), Kaiko told a new story he had never told before during the protracted litigation in the *Boehringer-Ingelheim* and *Endo* cases.

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Kaiko's recent testimony stands in stark contrast to testimony that he has given on this subject on several prior occasions:

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(3) Finally, at the trial in the *Endo* case, and on direct examination by Purdue's counsel, Kaiko was given free rein to describe the process by which he arrived at his insight

regarding the reduced dosage range of controlled-release oxycodone and the information that he considered. (Ex. 2, *Endo* Tr. at 168:8-177:5.) Kaiko confined his testimony to a discussion of the disadvantages of MS Contin[®] (its low bioavailability, etc.), the advantages of oxycodone (its high bioavailability, short half-life, etc.), and his survey of morphine, which purportedly established the eight-fold range required to control pain in 90% of patients. (*Id.*) Kaiko made no mention of any calculations of dosages of other opioids and degrees of pain control in individual patients at Sloan-Kettering. (*Id.*)

This stark about-face in Kaiko's testimony raises suspicions aplenty, which are only heightened by the fact that Purdue has been unable to produce a single document regarding Kaiko's purported surveys of dosages of morphine. *Endo*, 2004 U.S. Dist. LEXIS 10 at *71.

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Kaiko's recent testimony is simply not credible. Mallinckrodt submits that it represents an effort to explain away a misrepresentation that surveys were done when they were not. Moreover, because the statements about surveys are affirmative misrepresentations—and not merely omissions—regarding the existence of empirical support for the four-fold vs. eight-fold dosage range discovery, they supply the high level of materiality that the Federal Circuit

previously found wanting in the *Endo* case. Thus, the Court can find inequitable conduct here based on these affirmative misrepresentations alone.

B. Even ignoring Purdue's statements about "surveys," the Court can find intent based on the omission in the *Endo* case.

The above affirmative misrepresentations aside, the Court can find intent based solely on the omission discussed in the opinions in the *Endo* case in light of the following considerations, which were not addressed in the *Endo* opinions.

First—The language the inventors and their attorneys selected for use in describing the surprising discovery of a four-fold dosage for controlled-release oxycodone (versus eight-fold for the prior art opioid compositions) is probative of their intent. As the Federal Circuit has repeatedly held, intent may and often is proved by “a showing of acts the natural consequences of which are presumably intended by the actor.” *Merck & Co., Inc.*, 873 F.2d at 1422 (internal citation omitted). Davidson’s response to the first office action in the ‘331 prosecution provides a representative example of the choice of language. Davidson stated, as a matter of absolute, established fact:

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a *substantially narrower, approximately four-fold* (10-40 mg. every 12 hours - around-the-clock dosing) in approximately 90% of patients.

(Ex. 27, PTX 7 at ‘331-41 (emphasis in original).) In distinguishing the prior-art ‘341 patent that the examiner had relied on in his rejection, Davidson went even further:

It is respectfully submitted that one skilled in the art having knowledge of the controlled release oxycodone [*sic*—hydromorphone]...would not be motivated to prepare controlled release oxycodone formulations in a dosage range from about 10 mg to about 40 mg, which formulations thereby acceptably control pain over a *substantially narrower, approximately four-fold* range in 90% of patients...One skilled in the art *would certainly not arrive at this surprising result without the benefit of hindsight.*

(Ex. 27, PTX 7 at ‘331-43 (latter emphasis added).)

This repetition of similar statements implying established fact, always in quantitative numerical terms and often in the past tense throughout the prosecution of four patents, shows that the inventors and/or their attorneys intended to instill a belief in the mind of the patent examiner that the discovery of the four-fold dosage range was based on the results of clinical studies. Such a belief would be the “natural consequence” of the repeated statements of what the Purdue inventors had found. Even the prosecuting attorney Steinberg admitted that when a finding is described in the past tense it must be supported by “proof by comparative tests.” (Ex. 2, *Endo* Tr. at 1628:8-10 (Steinberg).) The “findings” here were not based on such proof, however, much as the inventors tried to make it sound like they were.

Second—the knowledge of those involved in drafting and prosecuting a patent application of their duty of candor is also probative of intent. *Digital Control, Inc. v. Charles Machine Works*, 437 F.3d 1309, 1319-20 (Fed. Cir. 2006). Davidson testified in *Endo* that he repeatedly advised the inventors of their duty of candor to the Patent Office. (Ex. 2, *Endo* Tr. at 1637:23-1638:10 (Davidson); *Id.* at 1594:4-1595:15 (Steinberg).)

Third—There is no question that Purdue had a motive to deceive the PTO. During the trial in *Endo*, every Purdue witness who was involved in the development of controlled-release oxycodone testified that Kaiko was the prime mover behind the project. Kaiko himself testified that, shortly after he arrived at Purdue in 1985, he presented the idea to one of Purdue’s owners. (Ex. 2, *Endo* Tr. at 167-68.) According to Oshlack, Kaiko “championed” the project “and the project became very active.” (Ex. 2, *Endo* Tr. at 484.) Purdue’s medical director, Goldenheim, agreed. (Ex. 2, *Endo* Tr. at 994.) Kaiko’s 1990 memorandum to Purdue’s top management continued to press the case for keeping controlled-release oxycodone as a priority R&D project, specifically citing the threat of generic competition for Purdue’s MS Contin®. (See Ex. 18, DTX

3165.) This product was Kaiko's pet, and he clearly set out to obtain patents covering the early T_{\max} pharmacokinetics of a twice-a-day oxycodone that could prevent any competitor from ever making any 12-hour controlled-release oxycodone of any type.

Fourth—As described in the remainder of this brief, the record shows other instances in which Purdue made material misrepresentations and withheld other material information in its dealings with the patent office. Intent to deceive the PTO may be inferred where there is a pattern of misrepresentation or concealment of material facts. *Paragon Podiatry Lab., Inc.*, 984 F.2d at 1193 (“The prosecution of the patent application in this case, viewed in its entirety, demonstrates an overriding pattern of misconduct sufficient to support the district court’s finding of culpable intent.”); *In re: ‘639 Patent Litigation*, 154 F. Supp. 2d 157, 194 (D. Mass. 2001) (“Beecham engaged in a pattern of misrepresentation in its dealings with the PTO so pervasive as to negate any possibility that Beecham’s misrepresentations to the PTO were inadvertent ‘loose language’ or otherwise negligently made.”); *Golden Valley Microwave Foods, Inc. v. Weaver Popcorn Co.*, 837 F. Supp. 1444, 1471 (N.D. Ind. 1992) (“The facts include too many instances of the withholding of material information for any conclusion to be reached other than that the withholding and mischaracterizations were done with the intent to mislead the Patent Office.”). Such a pattern is present here.

III. Purdue made numerous other material misrepresentations.

The record is replete with other material misrepresentations and omissions beyond those considered by this Court and the Federal Circuit in *Endo*. These provide additional support for findings of materiality and intent.

A. Purdue failed to disclose clinical data and other information from its clinical studies that contradicted its asserted patent claims.

The withholding of studies contradicting the representations regarding the purported benefits of the invention is powerful additional evidence of inequitable conduct not previously considered by this Court. While prosecuting the '295 and '912 patents, Kaiko knew about the tablet investigator report, the LoRusso study, and the Kalso study. In the preliminary tablet investigator report, *zero* of the 11 physicians surveyed found OxyContin® easier to titrate than MS Contin®. (Ex. 33, DTX 3739 at P 054893.) The LoRusso study likewise found that OxyContin® was not any easier to titrate than MS Contin®. (Ex. 34, PTX 717 at P 187373.) And the Kalso study concluded that the median number of days to achieve stable pain control was not significantly different with controlled-release oxycodone (3.0 days) and controlled-release morphine (1.5 days). (Ex. 38, DTX 4355 at P 642973.)

Kaiko knew about the tablet investigator study before any of the patents in suit issued, and he knew about all three studies while the '295 and '912 patents were pending. Yet he did not cite any of them to the PTO. Nor did he offer any credible explanation for his remarkable failure to do so. Kaiko said he did not disclose the OxyContin® tablet investigator preliminary report because it covered only 11 doctors. (Ex. 2, *Endo Tr.* at 345:2-345:16.) But Purdue sought out "high volume" investigators, and thus it is reasonable to conclude that each investigator administered the composition to at least several patients. (Ex. 32, DTX 3739 at P 054892.) And Kaiko's only explanation for failing to disclose the LoRusso and Kalso studies was they lacked methodological controls and as such did not conclusively disprove his hypothesis regarding dosage range and ease of titration. (Ex. 2, *Endo Tr.* at 250:24-251:16.)

Purdue is on the wrong side of the law on this issue. Rule 56 does not obligate one to disclose only data that *conclusively* disproves the assertions made in support of patentability. 37

C.F.R. § 1.56(b)(2) (2004). Rather, the materiality standard is satisfied if the information merely “refutes, or is inconsistent with, a position” the inventors took in asserting an argument of patentability, as these studies did. *Id.* It is enough if the data is directly related to an important issue of patentability, and even if the data presented a close case for disclosure (which here it did not), close cases must be resolved in favor of disclosure. *See Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1365-66 (Fed. Cir. 2007) (even if tests are performed under unusual conditions and are not comparable to data submitted to examiner, results are material because “[m]ateriality is determined from the viewpoint of a reasonable patent examiner, and not the subjective beliefs of the patentee. A reasonable examiner would certainly want to consider test data that is directly related to an important issue of patentability.” (internal citations omitted)); *see also Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1257 (Fed. Cir. 1997) (“close cases should be resolved by disclosure, not unilaterally by applicant.” (internal quotation omitted)). It is supremely ironic that Kaiko withheld from the PTO actual studies that contradicted his arguments in favor of patentability, but readily relied on vague anecdotal evidence of a purported “calculations” of dosages of opioids other than morphine as a substitute for the “surveys” that he admits he did not do.

The study results here were directly related to an important issue of patentability and contradicted Purdue’s express representation in the patents in suit of a decreased duration of “opioid analgesic titration process” with the patented oxycodone compositions. Purdue had an obligation to disclose these study results. Its failure to do so is additional evidence of its intent to deceive the PTO.

B. Purdue misrepresented to the PTO that controlled-release oxycodone having a T_{\max} between 2 and 4 hours and providing 12 hours of pain relief was a “surprising” discovery.

Purdue also intended to deceive the PTO in its repeated claims that findings were “surprising” when they obviously were not. In the ‘331 application, Purdue represented that “[t]he present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2-4 hours[†] after administration gives at least 12 hours pain relief.” (Ex. 27, PTX 7 at ‘331-7.) To support its claim of “surprise,” Purdue said that “it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4-8 hours after administration.” (*Id.*) Yet Purdue presented no evidence at trial of any extended-release composition having a T_{\max} at 4 to 8 hours and providing 12 hours of effectiveness.

In fact, the finding discussed in the application would not have been “surprising” to one of ordinary skill in the art. By the time Steinberg filed the ‘331 application, the representation of a “surprising” finding of an early peak plasma level and 12 hours of therapeutic activity had become a stock phrase for Purdue to use in applications for controlled-release opioids. Steinberg first used it in the application for the ‘984 dihydrocodeine patent in 1987. (Ex. 13, DTX 2047, the ‘984 patent at col. 2, lns. 18-21.) He repeated it verbatim in the application for the ‘909 and ‘341 hydromorphone patents in 1987 and 1989, respectively. (Ex. 15, DTX 2045, the ‘341 patent at col. 2, lns. 19-22; Ex. 14, DTX 2063, the ‘909 patent at col. 2, lns. 16-19.) He then

[†] For consistency and convenience, Mallinckrodt will refer to a 2-4 hours T_{\max} in this brief for both the ‘331 patent and the ‘912, ‘295, and ‘042 patents in suit. During the *Endo* trial, most of the witnesses discussed the peak plasma level as between 2-4 hours, regardless of whether it related to the ‘331 patent or the patents in suit. The ‘331 patent states that “[t]he present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief....” (Ex. 24, DTX 2044, the ‘331 patent, at col. 2, ln. 20-23.) The patents in suit, however, state that a peak plasma level at between “2-4.5 hours after administration” gives at least 12 hours pain relief....” (Ex. 29, DTX 2049, the ‘912 patent, at col. 5, ln. 11-12; Ex. 30, DTX 2059, the ‘259 patent, at col. 5, ln. 9-12; Ex. 31, DTX 2060, the ‘042 patent, at col. 5, ln. 11-14.) Kaiko admitted that the extra half hour in the patents in suit could be seen as “a capturing of the prior art.” (Ex. 2, *Endo* Tr. 376:22-377:6.)

repeated it verbatim again in the application for the '331 patent in 1991. (Ex. 24, DTX 2044, the '331 patent at col. 2, lns. 20-23.) He simply changed the name of the particular opioid.

During prosecution of the application for the '331 patent, the examiner twice rejected the claims as obvious over the '341 controlled-release hydromorphone patent in view of the '598 controlled-release oxycodone patent. (Ex. 27, PTX 7 at '331-34 - '331-36, '331-44 - '331-46.) Among other things, the examiner pointed out that the '341 patent disclosed "peak plasma levels attained between 2.25 and 3.75 hours [after administration]" and that "both oxycodone and hydromorphone being derivatives of natural alkaloids with many structural similarities are considered interchangeable in the matrix compositions." (Ex. 27, PTX 7 at '331-35 - '331-36). The examiner further noted that the '598 patent disclosed "matrix composition as those of applicants' wherein the active agent is oxycodone," *i.e.*, controlled-release oxycodone made with the AcroContin system, as did the application for the '331 patent. (Ex. 27, PTX 7 at '331-36.)

In response to the second office action, Steinberg filed Kaiko's declaration, which stated, in relevant part:

It is my opinion that one skilled in the art having information concerning the time to reach peak plasma concentration (hereinafter referred to as "the t_{max} ") and duration of effect for a controlled-release *hydromorphone* formulation as set forth in the Goldie, et al, 341 patent, could not predict whether a controlled-release *oxycodone* formulation having a t_{max} in 2-4 hours would also provide a duration of therapeutic effect of at least 12 hours.

(Ex. 27, PTX 7 at '331-54 (emphasis in original).) In support of his opinion, Kaiko argued that "[t]he relationship between the pharmacokinetics and pharmacodynamics of opioid analgesics is particularly complex and unpredictable because of many confounding factors." (*Id.*)

In making these representations, Steinberg and Kaiko withheld from the Patent Office the fact that, in addition to controlled-release hydromorphone, Purdue and its affiliate had developed several other controlled-release opioids characterized by a peak plasma level at between 2-4

hours and 12 hours of therapeutic activity. Kaiko knew that these prior-art opioid compositions shared these characteristics and testified at trial in *Endo* that his “lawyers appreciated this as well.” (Ex. 2, *Endo* Tr. at 369:2-370:5.) Nevertheless, neither Kaiko nor Steinberg brought this information to the attention of the examiner.

Kaiko’s failure to tell the examiner about the other controlled-release opioids is particularly egregious in light of the fact that, when he became involved in the development of controlled-release oxycodone, he told Oshlack that the objective was to duplicate the early peak plasma level of MS Contin[®], Purdue’s controlled-release morphine product exhibiting 12-hour pain relief. (Ex. 2, *Endo* Tr. at 177:18-178:21.)

If the prior art had contained no description of a controlled-release opioid composition with 12-hour effectiveness, one might have been surprised *the first time* one found that T_{\max} of such a composition is in the 2-4 hour range. But the *fifth time* one formulates a controlled-release opioid with these characteristics, can it really be a “surprise”? The examiner was entitled to know of these other controlled-release opioids so that *he* could determine whether the fifth time may be rightly called a “surprise.”

As above, selection of the word “surprising” here was no accident. The word was chosen to counter any suggestion that controlled-release oxycodone was unpatentable in light of the close prior art. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“[T]hat which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.”).

At trial in *Endo*, Kaiko tried to defend his withholding of information on codeine and dihydrocodeine on the ground that these drugs are not used for moderate to severe pain. (Ex. 2, *Endo* Tr. at 367:21-368:9.) This excuse was beside the point because the issue raised by the examiner did not concern degrees of pain. (Ex. 13, DTX 2047, the ‘984 patent at col. 1, lns. 5-

7.) Moreover, the '984 dihydrocodeine patent expressly states that dihydrocodeine is used to treat moderate to severe pain. And, Purdue's internal documents disclose that controlled-release codeine competed with oxycodone as analgesics prescribed for "moderate to moderately-severe cancer pain." (Ex. 31, DTX 3184 at P775189.)

Steinberg tried to explain his failure to disclose the '984 dihydrocodeine patent on the ground that it was cumulative. (Ex. 2, *Endo Tr.* at 1632:6-11.) But the issue before the examiner was obviousness, and the examiner had already fixed on the early T_{max} of the controlled-release hydromorphone as one of the points of commonality between the '341 patent and the '331 application. Clearly, the examiner considered early T_{max} to be a material consideration. The duty of candor requires that, rather than withhold a material reference, an applicant and counsel should disclose it and provide their explanation, if any, of the material information that is at odds with the applicant's claim of patentability. *See* 37 C.F.R. § 1.56(b) (2004); 4 Chisum on Patents § 11.03[4][b][v] (notes and accompanying text.)

C. Purdue presented Kaiko as an independent expert.

It was also deceptive for Kaiko and Purdue's attorneys to present Kaiko in a manner that would lead an examiner to assume that he was an independent expert. The '331 application and the '912, '042 and '295 applications all identify the assignee of the applications as Euro-Celtique, S.A., of Luxembourg. (*See* Ex. 29, DTX 2049, the '912 patent; Ex. 30, DTX 2059, the '259 patent; Ex. 31, DTX 2060, the '042 patent.) Euro-Celtique, S.A. is an affiliate of Purdue and served as the common owner of patent applications and patents on inventions made by Purdue and its affiliated companies. (Ex. 2, *Endo Tr.* at 1598:22-25.)

When, on March 23, 1993, Purdue's attorneys filed Kaiko's declaration in the '331 case, they did not disclose Purdue's relationship with Euro-Celtique. (Ex. 27, PTX 7 at '331-51.) They also did not disclose that Kaiko had collaborated with the inventors of the '331 application

in developing controlled-release oxycodone, and that four months earlier they had filed the '912 application relating to controlled-release oxycodone.

Having worked with Kaiko on the application for the '912 patent, he also knew of Kaiko's intimate involvement in the controlled-release oxycodone project.

Although Davidson knew these facts, he drafted a declaration that presented Kaiko as an independent, unbiased expert. (Ex. 27, PTX 7 at '331-51 - '331-56.) In the declaration, Kaiko identified himself as Vice-President, Clinical Research, for the Purdue Frederick Company. (*Id.* at '331-51.) Kaiko described in detail his academic training, his research and academic appointments, his activities in several scientific and medical societies and governmental organizations, and his scientific publications. (*Id.* at '331-51 - '331-53.) Kaiko then averred that "I believe that my experience as detailed above and in my attached curriculum vitae establishes me as an expert in the pharmacology of opiate analgesics." (*Id.* at '331-53.) Then, employing the language that is commonly used in reports by independent experts, Kaiko averred in his declaration that he "[had] reviewed and [was] familiar with the subject matter and claims of" the '331 application, the '341 patent and the '598 patent. (*Id.* at '331-53.)

It has long been held that, where, as here, an applicant for a patent responds to an obviousness rejection with a declaration stating an opinion that the invention is not obvious, any bias on the part of the declarant is a matter for the examiner's consideration. *See In re McKenna*, 203 F.2d 717, 720 (C.C.P.A. 1953). Even in the absence of a specific request by an examiner for a declaration, a failure to disclose the declarant's interest has been held material and done with intent to deceive. *Nilssen v. Osram Sylvania, Inc.*, 440 F. Supp.2d 884, 901 (N.D. Ill. 2006);

Baxter Diagnostics, Inc. v. AVL Scientific Corp., 924 F. Supp. 994, 1003-05 (C.D. Cal. 1996).

But the failure to disclose a declarant's interest is most insidious where, as here, the examiner has requested a declaration. *See, e.g., Paragon Podiatry*, 984 F.2d at 1191.

In this case, Davidson not only concealed the relationship between Kaiko's employer and the assignee Euro-Celtique, he also concealed Kaiko's deep involvement the controlled-release oxycodone project; concealed Kaiko's stake as an inventor in the related '912 application; and used language implying that Kaiko was an independent expert. These acts present compelling additional evidence of a clear pattern reflecting an overriding intent to deceive throughout the prosecution of the '331 patent and the '912, '295, and '042 patents in suit.

IV. Purdue's course of misconduct deprives it of any right to equitable enforcement of the patents in suit.

Where, as here, threshold showings of materiality and intent have been made, the court must then weigh its findings of intent and materiality to determine whether the equities warrant a conclusion that the patent is unenforceable. *Endo*, 438 F.3d at 1128; *see also Dayco Products, Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1364, n.3 (Fed. Cir. 2003) ("The court's authority to render a patent unenforceable for inequitable conduct is founded in the equitable principle that 'he who comes into equity must come with clean hands'" citing *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 814 (1945)).

Here there is ample evidence to establish a high level of both materiality and intent. At many critical points in the drafting and prosecution of the '331 patent and the patents in suit the inventors and their counsel chose, by different artifices, to hoodwink the Patent Office:

- Knowing they had no clinical studies showing the reduced four-fold dosage range of controlled-release oxycodone and the resulting ease of titration, Purdue selected language clearly implying clinical studies existed.

- Even assuming that Kaiko had done a survey or surveys of the dosage ranges of morphine, Purdue affirmatively represented that “surveys” of *other* opioid analgesics showed that they all required an eight-fold dosage range. It cannot have been the result of accident or negligence to leave the Patent Office with the mistaken impression that Purdue had empirical evidence showing both the disadvantages of the spectrum of prior-art controlled-release opioids and the advantages of the invention.
- When Purdue began to get results from clinical studies that contradicted its representations regarding the reduced dosage range and resulting ease of titration, Purdue withheld those studies from the Patent Office.
- When Purdue filed the ‘331 application, it disclosed the ‘341 controlled-release *hydromorphone* patent as relevant prior art, but not the ‘598 oxycodone patent—leaving it to the examiner to find it if he could. Although the examiner had cited the ‘598 patent in support of his obviousness rejection in the ‘331 prosecution, Purdue *again* omitted the ‘598 patent in the applications for the patents in suit.
- When, in response to a request from the examiner in the ‘331 prosecution, Purdue filed the declaration of Kaiko, Purdue not only failed to identify Kaiko’s bias, but also couched his declaration in language calculated to lead the examiner to believe that Kaiko was an independent neutral expert.
- And, characterizing as a “surprising discovery” that controlled-release oxycodone with an early peak plasma level provided 12 hours of pain relief, Purdue withheld from the Patent Office the fact that controlled-release oxycodone was the *fifth* controlled-release opioid that Purdue had developed that shared those features.

There are no accidents here. This evidence, considered in its entirety, establishes such a pervasive course of misleading conduct that the Court should declare the patents unenforceable.

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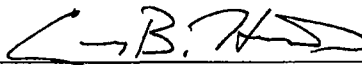
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CERTIFICATE OF SERVICE

Casey B. Howard hereby certifies that on the 21st day of September, 2007, he caused to be served unredacted copies of MALLINCKRODT'S BRIEF ON THE UNENFORCEABILITY OF U.S. PATENT NOS. 5,549,912, 5,656,295, AND 5,508,042 DUE TO INEQUITABLE CONDUCT and the supporting Declaration by Casey B. Howard with attached exhibits by having a true and correct copy thereof sent via Federal Express to:

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